REMARKS/ARGUMENTS

Claims 31, 33, and 37 have been amended to address issues raised by the Examiner regarding indefiniteness. Thus claim 31 has been amended to provide proper antecedent basis, and claims 33 and 37 have been amended to clarify that the particular IL-2 dosing regimen (daily in claim 33; three times per week in claim 37) begins on day 8 and lasts for 4 weeks. Support for these amendments can be found throughout the specification and in the original claims. Therefore, no new matter has been added by way of claim amendment.

Claims 20-44 are now pending in the application. Reexamination and reconsideration of the claims is respectfully requested in view of the following remarks. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

The Rejections of the Claims Under 35 U.S.C. §112 Should Be Withdrawn

Claims 36-38 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. This rejection is respectfully traversed.

Support for the "three times per week" dosing regimen for IL-2 or variant thereof resides in original claim 19 and in the detailed description of the invention beginning on page 12, line 27, continuing through page 13, line 9. Applicants respectfully submit that the requirement for sufficient written description has been met and no new matter has been recited by way of presentation of these claims. Accordingly, this rejection should be withdrawn.

Claims 31-34 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, claim 31 is rejected for lacking antecedent basis. Claim 31 has been amended to recite the phrase "wherein said method comprises," which provides proper antecedent basis. Accordingly this rejection has been obviated.

Claims 33 and 37 (and consequently the dependent claims) are rejected as being confusing. Claims 33 and 37 have been amended to clarify the day in which the IL-2 dosing regimen starts. Support for this amendment resides in claims 32 and 36. Applicants respectfully submit that these claims are definite, and this rejection should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 20-44 are rejected under 35 U.S.C. §103(a) in view of Grillo-López, U.S. Patent No. 6,455,043 (hereinafter, the "'043 patent") or WO 00/09160, the corresponding international patent application publication, in view of Applicants' admission on page 18, line 11, continuing through page 21, where variants of IL-2 known in the art are disclosed. This rejection is respectfully traversed.

The '043 patent and WO 00/09160 are directed to therapies using the Rituxan® antibody in combination with various other therapeutic agents for treatment of B-cell lymphomas. Where the Rituxan® antibody is to be administered with at least one cytokine, the list of which includes IL-2, these two cited references reportedly provide "a method for treating B-cell lymphoma comprising administering a synergistic therapeutic combination comprising at least one anti-CD20 antibody and at least one cytokine, wherein the therapeutic effect is better than the additive effects of either therapy administered alone" ('043 patent, col. 3, lines 26-31; WO 00/09160, page 45, claim 12). A key element serving as a basis for this rejection is the disclosure within the '043 patent and its corresponding WO publication that, with respect to the IL-2 plus Rituxan® combination, "a Phase I trial has been initiated in collaboration with the FHCRC to evaluate the safety and potential efficacy of a combined therapeutic regimen," and "[a] separate Phase II study is also being performed to evaluate the efficacy and the incidence of HACA formation in patients receiving low-dose IL-2 and Rituxan®" (col. 15, lines 25-31, of the '043 patent; page 28, lines 7-11, of the WO publication).

These two cited references provide a brief overview of the prior art status of use of IL-2 to treat advanced cancer and high-grade lymphoma. See the '043 patent at col. 14 and WO 00/09160 at pages 26-27. However, Applicants respectfully submit that the IL-2 doses discussed in '043 patent and corresponding WO publication are doses to be administered when IL-2 *is administered as a single agent*; there is no teaching or suggestion whatsoever in the '043 patent or corresponding WO publication as to what specific doses of IL-2 and Rituxan® should be administered *in combination* to achieve a safe and efficacious result with respect to treatment of B-cell lymphomas. These two cited references provide no details regarding dose of IL-2 and dose of anti-CD20 antibody that are to be administered *in combination* in the alleged Phase I and

Phase II clinical trials disclosed therein. In fact, Applicants submit that these two cited references do not provide enabling disclosures for treatment of any cancer using combination therapy with IL-2 and Rituxan®, much less enabling disclosures for a method of treatment wherein a "synergistic therapeutic combination" of these two agents is administered.

Applicants have previously argued in the Amendment filed April 1, 2004, that a mere suggestion to use the IL-2 plus Rituxan® combination for treatment of B-cell lymphomas without providing guidance as to what doses of these agents should be administered *in combination* cannot render obvious the therapeutically effective doses and dosing regimens presently claimed, particularly where two therapeutic agents each have known undesirable side effects. The Examiner has reasoned that Applicants arguments regarding unpredictability of combination therapy are rendered moot in view of the ongoing Phase II trials disclosed in these two cited references (see the Office Action mailed May 3, 2004, at page 7, lines 5-6). Applicants respectfully disagree for the following reasons.

In making this obviousness rejection, the Examiner relies on the statements within these two cited references regarding clinical trials being underway to investigate combination therapy with IL-2 and Rituxan®. Applicants have duly searched the Medline database and FDA clinical trial databases (*clinicaltrials.gov* and NCI's *cancer.gov*), and online Current Controlled Trials *meta*Register of Controlled Trials (a major international searchable database of archived and ongoing randomized controlled trials in all areas of healthcare, built by combining registers held by public, charitable, and commercial sponsors of trials) for a disclosure of the IL-2+Rituxan® clinical trials that are referred to in the '043 patent and WO 00/09160. Applicants cannot find any publicly available report of any clinical trial combining IL-2 and Rituxan® that can be attributed to the inventor (Grillo-López) of the '043 patent, the assignee thereof (i.e., IDEC Pharmaceuticals Corporation), or the collaborating agency, FHCRC (Fred Hutchinson Cancer Research Center), even though the Examiner asserts that Grillo-López conducted clinical trials on this therapeutic combination. The lack of any such public disclosure at the very least raises the question as to the status and/or existence of these alleged clinical trials.

Further, Applicants provide herewith the following Rituxan® review article for which the inventor of the '043 patent is the author: *"Rituximab (Rituxan®/MabThera®): The First Decade*

(1993-2003)," *Expert Ref. Anticancer Ther.* 3(6):767-769 (2003), a copy of which is submitted concurrently herewith as Appendix A. In this review article, Grillo-López provides a current (i.e., as of the writing of this 2003 review article) overview of clinical research conducted with Rituxan®. In the section outlining combination therapies, Grillo-López summarizes results for three combination studies, i.e., Rituxan®+CHOP, Rituxan®+IFN, and Rituxan®+ibritumomab tiuxetan (i.e., IDEC-Y2B8). The author refers to use of IL-2 in combination with Rituxan® only in the context of future avenues of research, stating "Other promising rituximab combinations include interleukin-2, granulocyte-macrophage colony-stimulating factor, alemtuzumab . . . and epratuzumab" (page 772, col. 2, first full paragraph, lines 5-9). However, Grillo-López provides no indication that he is aware of any such trial being underway with the IL-2+Rituxan® combination.

While an expert in the field of cancer research will not necessarily be aware of every clinical trial currently in progress, Applicants respectfully submit that such an expert should be aware of clinical trials that he referred to in his own patent. Applicants respectfully submit that if the IL-2+Rituxan® clinical trials referred to in the '043 patent and corresponding WO publication had actually been underway at the time of the filing of these cited documents (i.e., *August 11, 1999*), Grillo-López would not, in a 2003 Rituxan® review article, have referred to IL-2+Rituxan® combination therapy in the context of a discussion of <u>future</u> clinical development; rather, he would have either provided the results of one or both of these trials or would have referred to such trials as ongoing.

There are at least three possible reasons why Grillo-López fails to mention the specific trials directed to the IL-2+Rituxan®combination that he alludes to in his '043 patent and corresponding WO publication, which were based on a provisional patent application filed <u>five</u> years prior to publication of this review article: (1) the ongoing clinical trials have yet to be completed, and he is not at liberty to elaborate for fear of compromising the results; (2) the clinical trials failed to yield safe and efficacious results; or (3) the clinical trials have yet to be undertaken. If the first possibility is true, then a record of these trials recruiting enrollment of patients should be publicly available; as noted above, Applicants have duly searched and cannot find any such record. If the second or third possibility is true, then these two cited references

cannot serve as the basis of an obviousness rejection; neither of these references, alone or in combination, provides any guidance whatsoever as to what doses of IL-2 should be used in combination with Rituxan® to treat B-cell lymphomas.

Applicants respectfully submit that there is sufficient evidence outlined above to bring into question whether the IL-2+Rituxan® clinical trial trials referred to in the '043 patent and corresponding WO publication were ever conducted, or, if they were conducted, whether safe and efficacious results were actually obtained. Unless the Examiner can cite to where these alleged Phase I and Phase II clinical trials are being conducted and by whom, the preponderance of evidence lies in favor of Applicants' contention that these trials were never conducted. A statement regarding non-existent clinical trials and non-existent data cannot properly serve as a basis for rendering moot the issue of unpredictability in combination drug therapy.

The Examiner asserts that it is obvious to try combination therapies to treat the same disease. However, even in light of these two cited references, the skilled artisan is not guided to safe and efficacious doses of the combination of these two drugs, much less the optimal dosages. These references merely invite experimentation; yet an invitation to experiment is not sufficient grounds to reject an invention as obvious for reasons outlined in Applicants' Amendment filed April 1, 2004.

As Applicants have previously noted, the therapeutic outcomes of drug combinations cannot be predicted with any reasonable expectation of success, especially when both drugs have undesirable side effects. In fact, experimentation with drug combinations in clinical trials ensures a reasonable chance of safely and efficaciously treating with the drug combination. Moreover, the protocols of such drug combination experiments are in the form of dose escalation, not "optimization" as the Examiner contends. Dose optimization (formulation of the most efficacious dose with least side effects) only occurs once the toxicology/safety (Phase I trials) and efficacy (Phase II trials) data are known. Applicants again point out that at the time the present application was filed, Applicants provided the first and only clinical data regarding efficacy and safety of IL-2 and Rituxan® combination therapy for treatment of B-cell lymphomas. Applicants are the first to discover the therapeutic doses that achieve clinical

efficacy and safety. Since these data were unknown prior to Applicants' disclosure, the therapeutically effective amounts disclosed by Applicants are non-obvious.

Furthermore, the fact that variants of IL-2 were known in the art at the time of Applicants' invention does not provide any suggestion as to what doses of anti-CD20 antibody or fragment thereof and IL-2 or variant thereof should be used in combination to treat human subjects with non-Hodgkin's B-cell lymphomas. This missing information is not taught or suggested in the cited '043 patent or WO 00/09160 publication.

In view of these remarks, Applicants respectfully submit that these two cited references alone or in combination with "Applicants' admission" as to known IL-2 variants do not teach or even suggest all of the claim limitations, nor do they provide to one of skill in the art a reasonable expectation of successfully modifying the teachings of these cited references to arrive at Applicants' claimed invention. As such, a *prima facie* case of obviousness has not been established, and this rejection of the claims should be withdrawn.

CONCLUSION

In view of the aforementioned amendments and remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. §112, first and second paragraphs, and §103(a) are now overcome. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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